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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,957	HERWEIJER ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-12,25-27,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-12,25-27,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 23 November 2005 in reply to the Final Action mailed 7 September 2005. Claims 1-7, 9-12 and 25-27 were considered in the 7 September Office Action. Claims 1 and 25 were amended and claims 34 and 35 were added in the 23 November Paper. Claims 1-7, 9-12, 25-27, 34 and 35 are pending and under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 November 2005 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment and Arguments

Claim Objections

Objection to claim 1 as being informal is withdrawn in view of the amendment thereto.

Claim Rejections - 35 USC § 112

Rejection of claims 1-7 and 8-12 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "a majority of mammals injected" is **withdrawn** in view of the

amendment of the claim such that it recites that the immune response is generated in a majority of "individual mammals injected".

Claims 25-27 **stand rejected** under 35 U.S.C. 112, second paragraph, as being indefinite in reciting expressing antigen "in a majority of the injected rodents" (independent claim 25) for reasons of record.

As stated in the previous Office Action, is unclear from the disclosure whether this phrase requires that the immune response or expression be generated in a majority of rodent species or strains of mice, or whether the limitation requires that the majority of subjects within a treated population of a single species or strain exhibit an immune response or antigen expression.

Response to Arguments

In the remarks, page 12, Applicant contends that the claims have been amended to recite "generating the immune response in a majority of individual mammals injected". However, no such amendment has been made to claim 25. Therefore, Applicant's arguments are not persuasive with respect to claims 25-27.

Claims 1-7, 9-12 and 25-27 **stand rejected** and newly added claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention for reasons of record and herein below. This is a new matter rejection.

As stated in the previous Office Action, the Examiner can find no literal support for a process limited to generating an immune response in a majority of mammals injected or expressing antigen in a majority of injected rodents in the originally filed application. The closest teaching is found in Example 8, wherein eight mice were immunized with a plasmid encoding a luciferase transgene and an antibody response was detected in a majority of the mice injected (see also Figures 3 and 4). However, there is nothing in this teaching that would lead the skilled artisan to the more generic limitations now recited in the claims because the specification does not disclose obtaining an immune response or antigen expression in a majority of injected mammals or rodents as a general property of the disclosed method. In the absence of such generic teaching, the skilled artisan would not have viewed the specific example of an antibody response elicited in a majority of mice injected with a plasmid comprising a luciferase transgene as clearly conveying the limitation of a process to obtaining any immune response other than an antibody response in a majority of mammals (regardless of how the limitation is construed, *Id.*) or to obtaining an antibody response in a majority of any species of mammal other than a mouse injected with a construct comprising a luciferase transgene. Likewise, the skilled artisan would not have viewed the example as supporting claims limited to a process wherein a nucleic acid is delivered to a liver cell, wherein antigen is expressed in a majority of injected rodents. Therefore, the limitation of the claims to generating an immune response "in a majority of mammals" or expressing antigen "in a majority of the injected rodents" constitutes impermissible new matter.

Response to Arguments and the Declaration under 37 CFR 1.132

In response to the *prima facie* rejection of record, Applicant contends that the application teaches that the invention is intended for genetic vaccination, antibody production and isolation of antibody producing cells. Applicant urges that each of the stated intentions, especially genetic vaccination, would be readily recognized by those skilled in the art, as requiring that the process be effective in a majority of the mammals treated and, therefore, generating an immune response in a majority of individual mammals is inherently supported in the specification. Applicant has additionally submitted a declaration describing experiments performed with mice, rats and rabbits demonstrating generation of an immune response in a majority of individuals immunized according to the methods of the instant application. In the remarks bridging pages 6-7, Applicant states that the declaration additionally demonstrates gene delivery in dog, pig and primate; however, the Examiner is unable to find data for dog, pig, and primate in the Declaration.

Applicant's arguments and the showings of the declaration have been fully considered but are not deemed persuasive. The question at issue is whether the disclosure would have conveyed to the skilled artisan the claimed method limited to generating an immune response in a majority of individual mammals injected. Applicant's argument appears to be that, because generation of an immune response in a majority of mammals injected would be desirable for the applications contemplated for the method, the limitation of the method to only generating an immune response in a majority of mammals injected is implicit in the disclosure. This argument is not deemed persuasive because, although the skilled artisan might feel that it is desirable to obtain a positive outcome in more than half of the mammals treated, the disclosure by no means conveys the idea that obtaining an immune response in the majority of mammals injected is

required for the uses contemplated in the application. Logically, the skilled artisan would find it desirable to obtain an immune response in as many of the injected animals as possible. However, the instant claims specifically require that a positive outcome be obtained in greater than half of the animals injected. Nothing in the disclosure would lead the skilled artisan to believe that the limitation greater than half is more critical than would be the limitation greater than 40% or greater than 60%. Therefore, the disclosure does not convey to one of ordinary skill in the art the method particularly limited to obtaining an immune response in greater than half of the animals injected as recited in the claims.

The showings of the declaration are not persuasive, at least, because they are not disclosed in the application. Therefore, they cannot be used to establish what was described by the application as originally filed. Furthermore, the showings of the declaration merely provide examples of additional experiments wherein more than half of injected mice, rats and rabbits exhibited an immune response. However, even if the data had been presented in the application, the data would not have conveyed a specific lower limit for a positive outcome of ½ as recited in the instant claims. Therefore, the claim limitations would not have been supported by the data presented in the declaration even if it had been present in the application as filed.

Applicant's arguments and the showings of the declaration have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims are properly rejected under 35 USC 112, first paragraph, as containing new matter.

Claim Rejections - 35 USC § 102

Rejection of claims 1-6 and 9-12 under 35 U.S.C. 102(b) as being anticipated by either one of Liu *et al.* or Zhang *et al.* for reasons of record is **withdrawn** in view of the amendment of the claim 1 such that the method comprises isolating antibodies from the mammals.

Claims 25-27 **stand rejected** under 35 U.S.C. 102(b) as being anticipated by Hurpin *et al.* (1998) *Vaccine* 16:208-215 (made of record in the IDS filed 12 January 2005).

As stated in the previous Office Action, Hurpin *et al.* teaches a method of generating antibodies specific to an antigen (*i.e.,* p53) comprising providing a nucleic acid encoding said antigen (*i.e.*, a canary pox vector (ALVAC) comprising the nucleic acid) and injecting the nucleic acid into the tail vein of a rodent (see especially the first full paragraph in the right column on page 209 and the first full paragraph in the right column on page 210). Hurpin *et al.* further teaches that the ALVAC vector provides expression in the liver (see especially the second full paragraph on page 210 and Table 1) and assays for anti-p53 antibodies in the immunized mice, which would include the step of isolating said antibodies from said mouse. Therefore, the method of Hurpin *et al.* comprises each of the process steps of the instant claim 25 and is practiced with a mouse according to claim 27. Furthermore, the canary pox vector comprises the vector nucleic acid complexed with viral proteins, which viral proteins are polymers according to the limitations of claim 26.

Response to Arguments

In response to the *prima facie* case of record, Applicant has amended claim 25 to recite providing a nucleic acid "wherein the nucleic acid is either naked nucleic acid or is associated with a non-viral particle". Applicant contends that the teachings of Hurpin *et al.* do not apply to the claims because, "Hurpin *et al.* did not teach injection of a nucleic acid that was not associated with an intact virus" (page 5 of the Remarks).

This argument has been fully considered but is not deemed persuasive because it is based on an overly narrow reading of the claims. The claim does not recite that the nucleic acid is not associated with an intact virus. Instead, the claim states that the nucleic acid "is associated with a non-viral particle". There is no limiting definition of "associated with" or "non-viral particle" in the application. Therefore, the limitation is broadly construed as encompassing any particle that is non-viral, wherein the particle is anywhere in the vicinity of the nucleic acid. For example, the nucleic acid of Hurpin *et al.* was delivered in a solution that would comprise water particles, which water particles are reasonably construed as within the scope of non-viral particles. Therefore, the method of Hurpin *et al.* still comprises all of the limitations of the instant claims 25-27.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC 102(b) as anticipated by the art.

Claim Rejections - 35 USC § 103

Rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Liu *et al.* or Zhang *et al.* and further in view of Smyth-Templeton *et al.* is **withdrawn** in view of the

amendment of the claim 1 such that the method comprises isolating antibodies from the mammals.

New Grounds Necessitated by Amendment

Claim Rejections – 35 U.S.C. §112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-12, 25-27, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 34 and 35 are indefinite because there is no antecedent basis for the limitation "the immune response" recited in part (e), line 1. Amending claim 1 to recite "an antibody response", and amending claims 34 and 35 to recite "an immune response" instead of "the immune response" would be remedial.

Claims 2-7 and 9-12 are indefinite insofar as they depend from claim 1.

Claim 25 is indefinite in the recitation of "associated with" in line 4. There is no limiting definition of "associated with" in the application as filed and it is unclear what is meant by association with a non-viral particle. For example, must the non-viral particle be in physical contact with the nucleic acid or is it sufficient that the non-viral particle be somewhere in the vicinity of the nucleic acid? If the latter is the case, must the non-viral particle be contained within a complex that comprises the nucleic acid or is it sufficient that the non-viral particle be anywhere in the vicinity of the nucleic acid? In addition, association with a non-viral particle

might also be construed as encompassing some type of association with a non-viral particle other than physical association. For example, is a nucleic acid that encodes non-viral particle within the scope of a nucleic acid "associated with" a non-viral particle because it can direct the synthesis of a non-viral particle? As the limitation "associated with" is subject to a variety of possible interpretations and the disclosure does not provide the means to distinguish what is embraced by the limitation from what is not embraced by the limitation, the metes and bounds of the claim are unclear.

Claims 26 and 27 are indefinite insofar as they depend from claim 25.

Claim 34 is additionally indefinite because there is no antecedent basis for "said antigen" recited in line 3 of the claim.

Claim 35 is additionally indefinite because there is no antecedent basis for "said mammals" in line 5 of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by either one of McCluskie *et al.* (1999) *Mol. Med.* 5:287-300 or Fynan *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:11478-11482 as evidenced by Liu *et al.* (1999) *Gene Ther.* 6:1258-1266 (previously made of record).

Claim 25 is directed to a method of generating antibodies specific to an antigen comprising: providing a naked nucleic acid sequence encoding a peptide containing at least one antigenic determinant operably linked to one or more control sequences; injecting said nucleic acid sequence into a tail vein of rodents thereby delivering said non-viral nucleic acid to a liver cell wherein the antigen is expressed in a majority of the injected rodents and an immune response directed against the expressed antigen is induced; and isolating antibodies specific to said antigen from said mammals.

McCluskie *et al.* teaches a method comprising providing a naked nucleic acid encoding the middle or major (S) surface proteins of the HBV envelope (see especially the second full paragraph on page 289) and injecting said nucleic acid into the tail vein of mice (see especially the paragraph bridging pages 289-290, the seventh line on page 290 in particular). Furthermore, McCluskie *et al.* teaches obtaining plasma from the injected mice and assaying the plasma for the presence of antibodies against the hepatitis B surface proteins (see especially the paragraph bridging pages 290-291 and Figure 1 and the caption thereto). The process of obtaining plasma from the injected mice would reasonably anticipate the step of isolating antibodies specific to the antigen claim. In addition, McCluskie *et al.* demonstrates antibodies specific for the antigen in 3 of 5 mice injected by the IV route (see especially Figure 1, upper panel). Therefore, the method of McCluskie *et al.* also comprises generating an immune response in the majority individual mammals injected. Although McCluskie *et al.* does not determine whether the nucleic acid is expressed in the liver, Liu *et al.* clearly demonstrates that tail vein injection results in delivery of nucleic acid to the liver (see Figures 1 and 2 of Liu *et al.*, which demonstrate transgene expression is achieved in liver even when low injection volume and relatively slow injection

times are used). Thus, absent evidence to the contrary, the skilled artisan would recognize that nucleic acid delivery to a liver cell would be inherent to the method of McCluskie *et al.*

Likewise, Fynan *et al.* teaches a method comprising providing a nucleic acid encoding the influenza virus hemagglutinin glycoproteins H1 or H7 (see especially the paragraph bridging pages 11478-11479) and injecting said nucleic acid into the tail vein of mice (see especially the first full paragraph on page 11479, line 17 in particular). Furthermore, Fynan *et al.* teaches obtaining plasma from the injected mice and assaying the plasma for the presence of antibodies against the hepatitis B surface proteins (see especially section entitled "Antibody Responses in DNA-Vaccinated Mice commencing on page 11480, Table 4 and the caption thereto). The process of obtaining plasma comprising antibodies specific to said antigen reasonably anticipates the step of isolating antibodies specific to the antigen. Although Fynan *et al.* does not explicitly disclose that an antibody response was obtained in a majority of the injected mice (the data in Table 4 are from pooled samples), Fynan *et al.* demonstrates protection from influenza challenge in 10 out of 12 mice injected by the IV route (see especially Table 1 and the caption thereto), which evidences an immune response in a majority of individual mice injected (see especially Figure 1, upper panel). Therefore, the method of Fynan *et al.* also comprises generating an immune response in the majority individual mammals injected. Finally, although Fynan *et al.* does not determine whether the nucleic acid is expressed in the liver, Liu *et al.* clearly demonstrates that tail vein injection results in delivery of nucleic acid to the liver (*Id.*).

Thus, the method of McCluskie *et al.* or Fynan *et al.* comprise each of the limitations of the instant claim 25 as evidenced by Liu *et al.* Therefore, the claim is anticipated by the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9-12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of McCluskie *et al.* (1999) *Mol. Med.* 5:287-300 or Fynan *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:11478-11482 in view of Liu *et al.* (1999) *Gene Ther.* 6:1258-1266.

Independent claim 1 is directed to a method of generating antibodies to a specific antigen in mammals comprising: providing a nucleic acid sequence encoding a peptide containing at least one antigenic determinant operably linked to one or more control sequences; injecting said nucleic acid sequence into a vessel connected to a tissue in said mammals; elevating intravascular pressure and increasing vascular permeability; generating an immune response in a majority of individual mammals injected; and isolating antibodies specific to said antigen from said mammals.

Independent claim 34 is directed to a method of vaccinating mammals comprising the steps as set forth in claim 1 with the exception that the method does not comprise isolating antibodies specific to an antigen, and independent claim 35 is directed to a method of generating immune cells that produce antibodies to a desired antigen comprising the process steps as set forth in claim 1 and further comprising isolating immune cells.

As described above, McCluskie *et al.* teaches a method comprising providing a naked nucleic acid encoding the middle or major (S) surface proteins of the HBV envelope (see especially the second full paragraph on page 289) and injecting said nucleic acid into the tail vein of mice (see especially the paragraph bridging pages 289-290, the seventh line on page 290 in particular). Furthermore, McCluskie *et al.* teaches obtaining plasma from the injected mice and assaying the plasma for the presence of antibodies against the hepatitis B surface proteins (see especially the paragraph bridging pages 290-291 and Figure 1 and the caption thereto). The process of obtaining plasma obtained from the injected mice would comprise both antibodies and immune cells that produce antibodies to the antigen. Therefore, obtaining plasma reasonably anticipates the step of isolating antibodies (claim 1) and immune cells that produce antibodies

(claim 35) specific to the antigen. In addition, McCluskie *et al.* demonstrates antibodies specific for the antigen in 3 of 5 mice injected by the IV route (see especially Figure 1, upper panel). Therefore, the method of McCluskie *et al.* also comprises generating an immune response in the majority individual mammals injected.

With regard to the method of claim 34, which recites that the mammals are vaccinated, the specification, at page 30, defines "vaccine" as "nucleic acids capable of directing the synthesis of one or more antigenic moieties, which is delivered into an organism to produce an immune response" and, at page 31, the specification teaches that "genetic vaccination" comprises an "immune response directed at proteins associated with conditions, infections, diseases or disorders such as allergens, pathogen antigens" etc. Thus, the broadest reasonable interpretation of the claim read in light of the specification encompasses any method comprising the recited steps wherein an immune response is generated against, *inter alia*, pathogen antigens. As McCluskie *et al.* clearly demonstrates both cellular and humoral immune responses against the pathogen antigen hepatitis B surface antigen, the method of McCluskie *et al.* provides vaccination according to the broadest reasonable interpretation of the claim.

Thus, the method of McCluskie *et al.* comprises each of the limitations of independent claims 1, 34 and 35 except for elevating intravascular pressure and increasing vascular permeability.

Fynan *et al.* teaches a method comprising providing a nucleic acid encoding the influenza virus hemagglutinin glycoproteins H1 or H7 (see especially the paragraph bridging pages 11478-11479) and injecting said nucleic acid into the tail vein of mice (see especially the first full paragraph on page 11479, line 17 in particular). Furthermore, Fynan *et al.* teaches obtaining

plasma from the injected mice and assaying the plasma for the presence of antibodies against the hepatitis B surface proteins (see especially section entitled "Antibody Responses in DNA-Vaccinated Mice commencing on page 11480, Table 4 and the caption thereto). The process of obtaining plasma comprising antibodies specific to said antigen reasonably anticipates the step of isolating antibodies and immune cells expressing antibodies specific to the antigen (*Id.*). Although Fynan *et al.* does not explicitly disclose that an antibody response was obtained in a majority of the injected mice (the data in Table 4 are from pooled samples), Fynan *et al.* demonstrates protection from influenza challenge in 10 out of 12 mice injected by the IV route (see especially Table 1 and the caption thereto), which evidences an immune response in a majority of individual mice injected (see especially Figure 1, upper panel). Therefore, the method of Fynan *et al.* also comprises generating an immune response in the majority individual mammals injected. In addition, as Fynan *et al.* demonstrates that the method provides protective immunity against influenza challenge, the method clearly provides vaccination as recited in claim 34.

Thus, the method of Fynan *et al.* also comprises each of the limitations of independent claims 1, 34 and 35 except for elevating intravascular pressure and increasing vascular permeability.

Liu *et al.* teaches a method of systemic administration of nucleic acids into mice via the tail vein comprising elevating intravascular pressure resulting in increasing vascular permeability (see especially the paragraph bridging the left and right columns on page 1265, and Figures 1-4 and 6-8). Furthermore, Liu *et al.* teaches that increasing intravascular pressure by increasing

injection volume and/or reducing injection time resulted in an enhancement of nucleic acid delivery and expression (see especially Figures 1 and 2 and the captions thereto).

The teachings of McCluskie *et al.*, Fynan *et al.* and Liu *et al.*, in combination, comprise all of the elements of the instant claims 1, 34 and 35.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of generating antibodies taught by McCluskie *et al.* or Fynan *et al.* to include elevating intravascular pressure and increasing vascular permeability according to the teachings of Liu *et al.* Motivation to combine these teachings is found in the nature of the problem solved in the methods of McCluskie *et al.* and Fynan *et al.*, which is to obtain an immune response against an antigen encoded by the injected nucleic acid, the general desirability of obtaining high level expression of antigen in a variety of tissues to generate a robust immune response, and the teachings of Liu *et al.*, which demonstrate that intravenous delivery comprising elevating intravascular pressure and increasing vascular permeability provides *in vivo* expression that is superior to intravenous delivery wherein intravascular pressure is not elevated. In particular, Liu *et al.* teaches that the level of transgene expression obtained by the method disclosed therein is among the highest ever achieved in the liver via systemic administration and that transgene expression was observed in all examined internal organs. See especially lines 15-21 on page 1264.

Absent evidence to the contrary, the skilled artisan would have a reasonable expectation of success in combining these teachings in view of the demonstration by McCluskie *et al.* and Fynan *et al.* that immunization can be achieved by the method disclosed therein and the demonstration by Liu *et al.* that the method can provide high-level transgene expression *in vivo*.

Thus, in view of the forgoing, the method of independent claims 1, 34 and 35, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims would also have been obvious to one of ordinary skill in the art based on the teachings of McCluskie *et al.* or Fynan *et al.* in view of Liu *et al.* for the reasons set forth herein above. As described above, each of the methods comprise tail vein injection of plasmid DNA in mice, which anticipates the limitations of dependent claims 9-12. Furthermore, Liu *et al.* teaches that delivery of plasmid DNA by the method disclosed therein provides transgene expression in all organs tested, including a liver cell according to claim 5 (see especially Figure 6 and the caption thereto). Given this wide distribution and absent evidence to the contrary, the skilled artisan would expect that the plasmid is also delivered to a lymphoid cell, according to claim 2, to a gut or nasal associated lymphoid cell, according to claims 3 and 4, and to a muscle cell according to claim 6.

Thus, in view of the forgoing, the method of claims 1-6, 9-12, 34 and 35, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103 as obvious over the art.

Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of McCluskie *et al.* (*supra*) or Fynan *et al.* (*supra*) as evidenced by Liu *et al.* (*supra*) as applied to claim 25 above in view of Smyth-Templeton *et al.* (1998) WO 98/07408 (previously made of record).

Claims 26 and 27 are directed to the method of generating antibodies of claim 25 described above, wherein the nucleic acid delivered is complexed to a polymer. The method of

generating antibodies is anticipated by McCluskie *et al.* or Fynan *et al.* as evidenced by Liu *et al.* for the reasons set forth herein except that the cited art teaches the method using naked DNA and not DNA complexed to a polymer.

Smyth-Templeton *et al.* teaches a polymeric lipid composition specially designed to improve delivery of intravenously administered nucleic acids to cells in animals (see especially the abstract and the paragraph bridging pages 3-4). Smyth-Templeton *et al.* teaches that lipidic particles increase the efficiency of DNA delivery into cells (see especially the paragraph bridging 1-2) and that the lipid formulations disclosed therein provide particularly efficient delivery of DNA administered intravenously (see especially the paragraph bridging pages 3-4 and Figures 1 and 2 and the captions thereto).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of McCluskie *et al.* or Fynan *et al.* to include complexing the administered plasmid with the protective polymeric coating of Smyth-Templeton *et al.* As described above, Smyth-Templeton *et al.* teaches that lipid complexes generally provide improved delivery of nucleic acids into cells, and that the formulations disclosed therein are particularly well suited for delivery of nucleic acids by intravenous administration. Given these teachings and the general desirability of obtain the most efficient delivery of DNA possible implied throughout each of the McCluskie *et al.*, Fynan *et al.*, Liu *et al.* and Smyth-Templeton *et al.* publications, the skilled artisan would be motivated to combine the teachings to provide improved efficiency of DNA delivery *in vivo*.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because Smyth-Templeton *et al.* demonstrates the effectiveness of

nucleic acid delivery using the complexes by tail vein injection in mice (see especially Example 4) and there is no reason to expect that nucleic acids used in the method of Liu *et al.* would not be operable when delivered using the complexes of Smyth-Templeton *et al.*

In view of these considerations, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made based on the teachings of McCluskie *et al.* or Fynan *et al.* in view of Smyth-Templeton *et al.*

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of McCluskie *et al.* (*supra*) or Fynan *et al.* (*supra*) in view of Liu *et al.* (*supra*) as applied to claim 1 above and further in view of Smyth-Templeton *et al.* (*supra*).

Claim 7 is directed to the method of generating antibodies described above, wherein the nucleic acid delivered is protected by a coating. The method of generating antibodies is obvious over McCluskie *et al.* or Fynan *et al.* in view of Liu *et al.* for the reasons set forth herein above. However, the cited art teaches the method using naked DNA and not DNA protected by a coating.

Smyth-Templeton *et al.* teaches a polymeric lipid composition specially designed to improve delivery of intravenously administered nucleic acids to cells in animals (see especially the abstract and the paragraph bridging pages 3-4). Smyth-Templeton *et al.* teaches that lipidic particles increase the efficiency of DNA delivery into cells (see especially the paragraph bridging 1-2) and that the lipid formulations disclosed therein provide particularly efficient delivery of DNA administered intravenously (see especially the paragraph bridging pages 3-4 and Figures 1 and 2 and the captions thereto).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of McCluskie *et al.* or Fynan *et al.* in view of Liu *et al* to include complexing the administered plasmid with the protective polymeric coating of Smyth-Templeton *et al.* As described above, Smyth-Templeton *et al.* teaches that lipid complexes generally provide improved delivery of nucleic acids into cells, and that the formulations disclosed therein are particularly well suited for delivery of nucleic acids by intravenous administration. Given these teachings and the general desirability of obtain the most efficient delivery of DNA possible implied throughout each of the McCluskie *et al.*, Fynan *et al.*, Liu *et al* and Smyth-Templeton *et al.* publications, the skilled artisan would be motivated to combine the teachings to provide improved efficiency of DNA delivery *in vivo*.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because Smyth-Templeton *et al.* demonstrates the effectiveness of nucleic acid delivery using the complexes by tail vein injection in mice (see especially Example 4) and there is no reason to expect that the elevated pressure used in the method of Liu *et al.* would in any way affect the complexes of Smyth-Templeton *et al.*

In view of these considerations, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made based on the teachings of McCluskie *et al.* or Fynan *et al.* in view of Liu *et al.* and further in view of Smyth-Templeton *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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